

REVIEW ARTICLE

Neurodegenerative Pathways in Alzheimer's Disease: A Review

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Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disease that leads to insidious deterioration of brain functions and is considered the sixth leading cause of death in the world. Alzheimer's patients suffer from memory loss, cognitive deficit and behavioral changes; thus, they eventually follow a low-quality life. AD is considered as a multifactorial disorder involving different neuropathological mechanisms. Recent research has identified more than 20 pathological factors that are promoting disease progression. Three significant hypotheses are said to be the root cause of disease pathology, which include acetylcholine deficit, the formation of amyloid-beta senile plaques and tau protein hyperphosphorylation. Apart from these crucial factors, pathological factors such as apolipoprotein E (APOE), glycogen synthase kinase 3 β , notch signaling pathway, Wnt signaling pathway, *etc.*, are considered to play a role in the advancement of AD and therefore could be used as targets for drug discovery and development. As of today, there is no complete cure or effective disease altering therapies for AD. The current therapy is assuring only symptomatic relief from the disease, and progressive loss of efficacy for these symptomatic treatments warrants the discovery of newer drugs by exploring these novel drug targets. A comprehensive understanding of these therapeutic targets and their neuropathological role in AD is necessary to identify novel molecules for the treatment of AD rationally.

ARTICLE HISTORY

Received: June 06, 2020
Revised: June 26, 2020
Accepted: July 31, 2020

DOI:
10.2174/1570159X18666200807130637

Keywords: Alzheimer's disease, neurodegenerative pathways, novel drug targets, acetylcholinesterase, glycogen synthase kinase, notch signaling, apolipoprotein E.

1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with no cure. It is the most common cause of dementia. There are about 40 million people with AD; most of them are above 65 years of age [1]. People affected with AD show disorientation, cognitive impairment, memory loss, behavioral changes leading to poor-quality life. The pathophysiology behind this disease is complex and not fully figured out. Leading causes behind the disease are found to be the increased activity of acetylcholinesterase, which eventually leads to a decrease in the levels of acetylcholine in the brain, hyperphosphorylation of tau proteins, the formation of senile plaques of A β and inflammation of neuronal cells in the brain [2]. Besides this, there are some other factors, which modulate the progression of AD, and they include genetic factors, apoptosis, mitochondria-mediated, atrophy, *etc.* These factors were figured out recently, and the recent studies

are rolling on these factors, how they are involved in the advancement of the disease, and their role in developing effective drugs for AD. Currently, there are only four drugs in the market that could be used for the treatment of AD, and they are donepezil, rivastigmine, galantamine and memantine. One more drug, tacrine, which was an acetylcholinesterase inhibitor, was withdrawn from the market due to its toxicity. These drugs can provide only symptomatic relief from the disease [3, 4]. One of the widely accepted mechanisms for AD development is considered to be low levels of acetylcholine in the brain due to increased acetylcholinesterase activity, eventually leading to progressive cognitive decline. The use of acetylcholinesterase inhibitors has been proved to be beneficial in improving the disease symptoms and also could reduce amyloid protein plaques.

In this context, extensive research has been carried out in search of promising acetylcholinesterase inhibitors that could be used in the treatment of AD. Recent advances in molecular modelling software enable the medicinal chemist to design novel molecules based on the three-dimensional structure of acetylcholinesterase. *In silico* docking studies trace out the drug-receptor interaction, which could be synthesized and evaluated for anti-Alzheimer's activity. Recent re-

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search in the field has made remarkable progress by identifying novel small molecules such as selenium-containing hydrochloride derivatives [5], triazole ring-containing compounds [6], chalcones [7], and sulfur-containing motifs [8] exhibiting remarkable acetylcholinesterase inhibitory activity. Fig. (1) shows significant changes in the brain during the progression of AD.

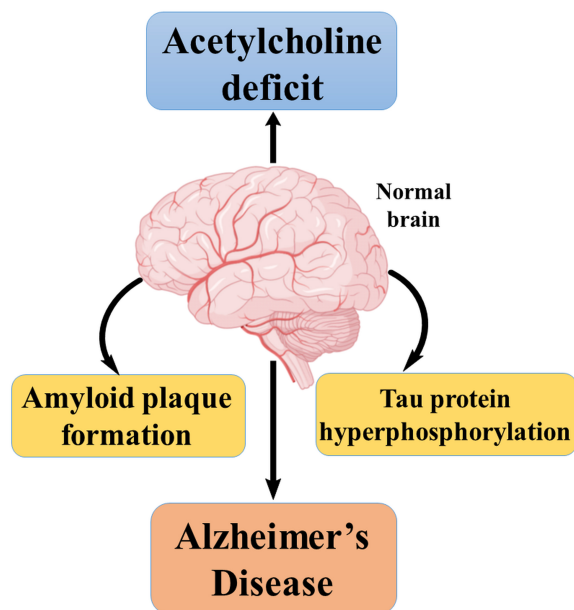


Fig. (1). Major hypotheses behind AD.

2. TYPES OF ALZHEIMER'S DISEASE

There are two primary forms of AD i) early-onset AD, ii) late-onset AD [9]. They are subdivided as sporadic as well as familial type. In most of the cases, AD happens after the age of 65. However, rarely AD occurs at an early age and known as early-onset AD or autosomal dominant AD (A-DAD). It is a rare type of AD and happens at the age of 30 to 50 years, and here comes the relationship between genetics and the occurrence of AD. Familial Alzheimer's disease (FAD) is another type of AD, which inherited through generations. It is also associated with genes and their mutations. Mutations to genes encoding presenilins and Amyloid Precursor Proteins (PSEN1, PSEN2 and APP) are responsible for the familial as well as early onset of AD. Presenilins (PES) is a significant component of γ secretase enzyme. Any change in the structure of the enzyme will impair the normal functioning of the same, which will promote the development of AD. Sporadic AD is a prevalent type, which does not pass through generations [10]. In this review, we will be discussing the various factors and pathophysiological markers behind AD.

3. NEUROLOGICAL PATHWAYS INVOLVED IN AD

3.1. Acetylcholine Esterase Inhibition

Earliest, the pathological factor behind AD is found to be acetylcholinesterase (AChE). There are two classes of cholinesterases, acetylcholinesterase and butyrylcholinesterase, in which acetylcholinesterase is located in the brain and neuronal synapses. Acetylcholine (ACh) is a neurotransmitter and plays an essential role in the neuronal transmission of impulses as well as learning and memory [11, 12]. According to the cholinergic hypothesis, an Alzheimer's brain shows a low level of acetylcholine, a neurotransmitter, happens when there is increased hydrolysis of ACh into acetate and choline in the presence of AChE [13]. According to the cholinergic hypothesis, AD brain shows low levels of ACh as well as it promotes the aggregation of $A\beta$, thereby the formation of senile plaques. Consequently, the inhibition of AChE could be considered as a promising approach for the treatment of AD [14]. Below Fig. (2) illustrates a pictorial representation of the relationship between AChE and AD [15].

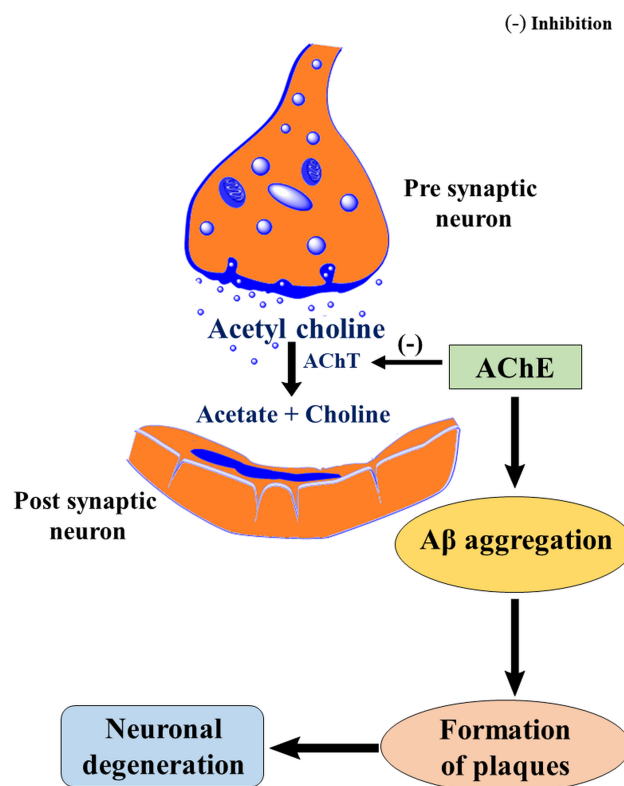
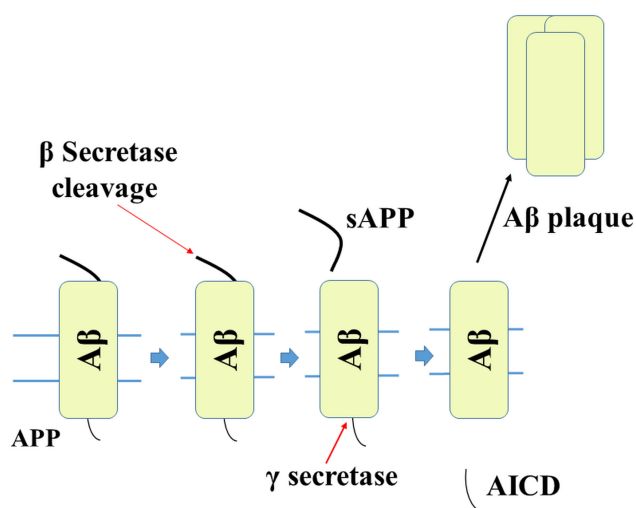


Fig. (2). Cholinergic hypothesis of neurodegeneration.

3.2. Amyloid Beta ($A\beta$) and the Role of APP in Alzheimer

Amyloid-beta deposits typically seen in the brain as senile plaques due to dysregulation of $A\beta$ lead to the formation of insoluble complexes, which get deposited in different

parts of the brain [16]. The deposition of A β is a significant risk factor in the inception and development of AD [17]. In healthy individuals, there will be the production of A β at a healthy level. However, in a diseased condition, there will be an overproduction of A β . It is usually produced from amyloid precursor proteins (APP) [18]. APP is a transmembrane protein, which is present in the brain at high levels and cleaved by different enzymes such as α , β , and γ secretases. In those enzymes, cleavage through β and γ secretases will lead to the formation of A β fragments [19]. A β formed will oligomerize and form plaques or complex structures. In a healthy individual, there will be a balance between the production and cleavage of A β in the brain. Impairment of this homeostasis will lead to the deposition of A β and plaques; ultimately, the dysfunction of the healthy brain [20, 21]. Fig. (3) shows the connection of APP with the formation of amyloid plaques [22].



APP – Amyloid precursor protein
sAPP - soluble APP

Fig. (3). Amyloidogenic pathway of APP.

3.3. Tau Proteins

The neuronal cytoskeleton has several components in which microtubules have a vital role in the formation of normal morphology of neurons, and they provide structural support for neurons [23]. Microtubules are generally made up of tubulin and tau proteins and are responsible for the production of microtubules from tubulin. Tau proteins belong to the category of Microtubular Associated Proteins (MAPs) [24].

Fig. (4) represents the role of tau protein and microtubules in disease progression. Usually, tau proteins bind to tubulin and are regulated by phosphorylation through kinases and phosphatases. But in pathological conditions like AD, tau proteins are abnormally phosphorylated, and lead to a de-

crease in binding with tubulin and thereby microtubule disorganization occurs, resulting in morphological changes in neuronal structure. Generally, the tau proteins self-polymerize and aggregate to form neurofibrillary tangles (NFTs) [25, 26].

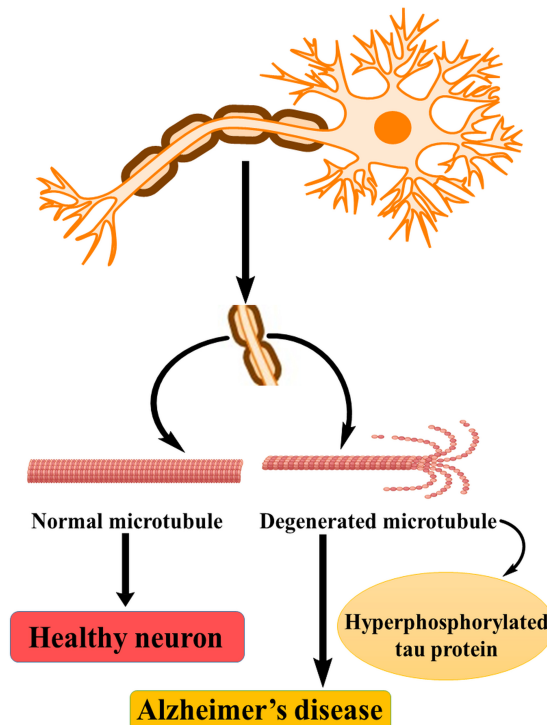


Fig. (4). Tau proteins and AD.

3.4. N-methyl-D-aspartate (NMDA)

Glutamate is the major excitatory neurotransmitter present in the mammalian brain, involved in the excitatory post-synaptic transmission of impulses *via* several receptors. In those, NMDA receptors are abundantly seen throughout the CNS [27]. NMDA receptors play a significant role in synaptic plasticity and cellular processes that form the basis for learning and memory. Therefore, the blockade of NMDA included in the potential disease-modifying treatment for AD. Various studies also point out the role of the *N*-methyl-D-aspartate receptor (NMDAR) in AD [28]. Fig. (5) demonstrates NMDAR and neuronal death are connected and lead to AD.

Normal essential functions of the central nervous system like neuronal development, synaptic plasticity, learning, memory formation *etc.*, are mediated by glutamatergic neurotransmission through NMDAR, which is an ionotropic glutamate receptor. It is found that overactivation of NMDAR leads to pathological excitotoxicity in neurological disorders such as AD [29].

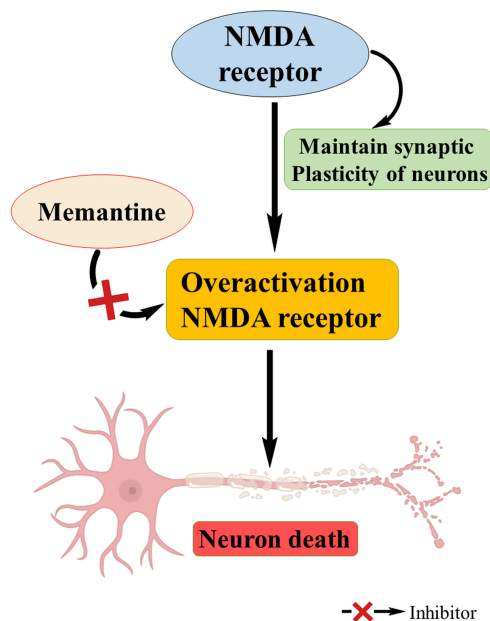


Fig. (5). Role of NMDA in AD.

Memantine, the only FDA approved NMDA receptor antagonist is active only at high concentrations of glutamate associated excitotoxicity of NMDARs, and they are ineffective at lower levels of the same. At standard conditions, channels for NMDA are open for several milliseconds, and memantine cannot act in this condition. However, during prolonged activation of NMDAR, it will work and accumulate in the channels and blocks the pathway [30].

3.5. Apolipoprotein (ApoE)

An arginine-rich protein seen in human plasma is associated with cholesteryl rich VLDLs. CNS ApoE is synthesized locally in the brain by astrocytes, microglial cells and neurons, and acts as a major transporter of cholesterol [31]. It is discoidal in shape and is synthesized in pathological as well as in physiological conditions. In Fig. (6), the relationship between ApoE and the formation of Aβ is depicted [32]. It is involved mainly in the regulation of the metabolism of lipoproteins [33]. ApoE encoded by a gene positioned on human chromosome 19 and variations in the gene sequence result in three alleles, namely ε2, ε3, and ε4. AD patients bear ApoE4 allele [34]. ApoE modulates morphology as well as homeostasis of the brain and thus holds a major role in ageing. ApoE may also regulate intracellular calcium levels [35].

3.6. Wnt Signaling Pathway

In AD brains, neurons undergo rapid apoptotic death. Wnt signaling pathway promotes the proliferation of progenitor cells typically during brain development [36]. β-amyloid proteins (βAP) induce changes to the Wnt signaling pathway and cause downregulation of the same, and this may lead to the formation of neurofibrillary tangles (NFT). As amyloid plaques and NFT are the histopathological hallmarks of AD,

the formation of NFT through impaired Wnt signaling pathway may promote the development of AD [37]. Below is the comparison between the roles of Wnt signaling in both regular and Alzheimer's condition (Fig. 7).

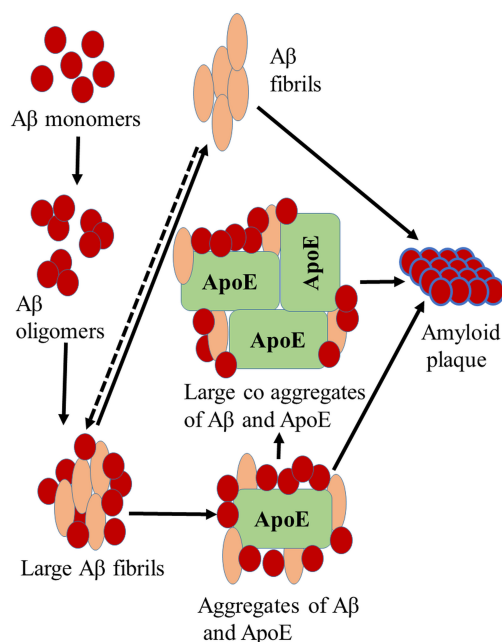


Fig. (6). ApoE and Aβ plaque formation.

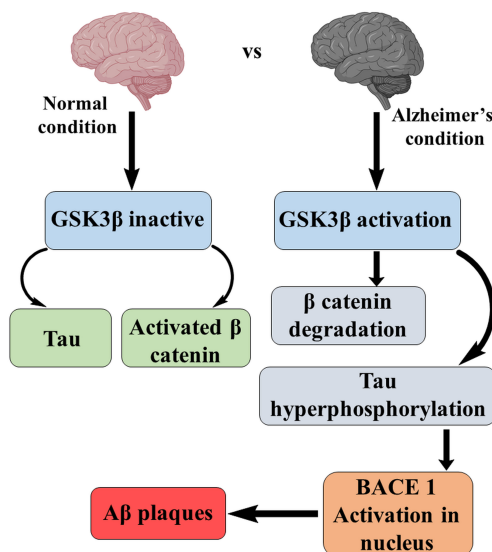


Fig. (7). Relation of Wnt signaling pathway with AD.

Wnt signaling pathway includes a variety of secreted glycoproteins like presenilins that involve in the proliferation and differentiation of neurons. Presenilin complexed with β-catenin, and GSK3β leads to the deposition of β-amyloid

(β A). They act as transducers in the Wnt signaling pathway. β -amyloid protein (β AP) induces the formation of NFT through the hyperphosphorylation of tau proteins with the help of enzymes like CDK5 and GSK3 β . GSK3 β acts as a vital component of the Wnt signaling pathway [38].

Besides, increased expression of p53 is seen in neurons impaired with β AP, and this may trigger apoptotic death of neurons and accordingly increase the expression of p53 in the BAX gene. Moreover, the Wnt pathway is negatively modulated by dickkopf-1 (DKK-1). The gene that encodes DKK-1 also targets p53. DKK-1 induces the downregulation of the Wnt signaling pathway [39].

3.7. Sirtuins and AD

Sirtuins are NAD⁺ dependent enzymes, having an essential role in age-related disorders. They come under the category of histone deacetylase (HDAC). Sirtuin 1 is the regulator of proteins and genes involved in different biological activities including antioxidant responses and anti-apoptotic responses, DNA repair and also it acts as the leading agent in maintaining synaptic plasticity and learning and memory [6]. The relation between sirtuins and the progression of AD is demonstrated by Fig. (8).

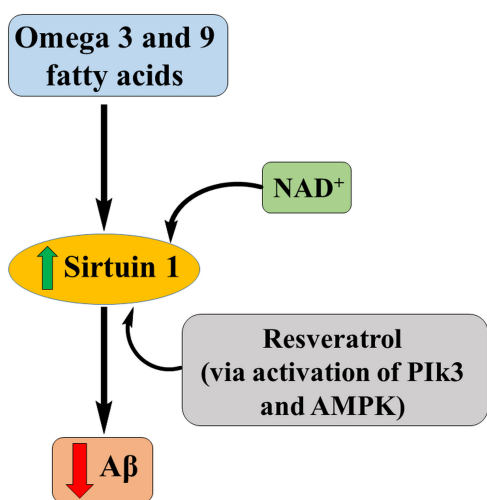


Fig. (8). Role of sirtuins in AD.

Calorie restriction (CR) is a regimen that increases the life span of animals in different ways, including reducing the usage of carbohydrates, reducing the production of ROS and thereby reducing the cell damage. CR needs some regulatory proteins such as sirtuins, a group of antiaging enzymes. Also, they are involved in different disease pathology, including diabetes, cancer, and neurodegenerative disorders like AD, Parkinson's and Huntington disease [40].

By activating sirtuins, we can attain either healthspan extension or a lifespan extension, which is highly associated with AD. Activated levels of sirtuins will reduce the forma-

tion of oligomerized A β . Activation of sirtuins can be done by two methods, either by using sirtuin-activating compounds such as resveratrol or by providing cellular NAD⁺ [41]. The most effective and general way involves the usage of direct NAD⁺ precursors like nicotinamide mononucleotide (NMN) or nicotinamide ribose to supply cellular NAD⁺. Resveratrol studies show better clearance of A β as well as the reduced formation of plaques. Resveratrol acts either directly or indirectly by activating AMPK and PIK3.

DNA impairment may cause the diminution of NAD⁺. Sirtuins and other DNA repairing enzymes use NAD⁺ as co-factor so that there will be depletion of NAD⁺ and loss of sirtuin function and leads to DNA damage [42].

3.8. mTOR

Mammalian target of rapamycin (mTOR) is a serine/threonine-protein kinase involved in the major biological processes such as protein translation and cell growth in response to different signals like growth factors, nutrient state and energy level [43].

At the cellular level, it is essential to keep the homeostasis in the body. Diseases like cancer and diabetes are characterized by impairment of mTOR signaling. It is also associated with neuronal activity, synaptic plasticity, and axon regeneration that is vital in the development of AD [44].

The mammalian target of rapamycin (mTOR) is a conserved protein kinase that plays a significant role in governing a balance between protein synthesis and degradation. It controls protein translation through phosphorylation reaction. It is directly linked to learning and memory [45].

mTOR is associated with different proteins and forms two complexes, mTORC1 and mTORC2. mTOR integrates these signals and controls ribosome biogenesis, transcription, translation and macroautophagy. Reducing mTOR signaling may have positive effects on age-related disorders, including neurodegenerative diseases. The level of mTOR increases the level of A β oligomers.

Complete blockage, as well as hyperactive mTOR signaling, worsens AD and results in impaired synaptic plasticity and learning and memory. Reduction of hyperactivity with specific agents like rapamycin may lead to improved synaptic plasticity, learning, and memory [46].

From the studies, it is evident that there is an optimum level of mTOR signaling, which is ideal for learning and memory. Any alterations in this will lead to a detrimental effect on learning and memory.

Hyperactive mTOR signaling may lead to the progression of tau pathology and thereby accumulation of the same through an increased translation of tau protein (Fig. 9). A β or tau accumulation produces mTOR hyperactivity, which may arbitrate neuronal death and A β -induced cognitive deficit [47].

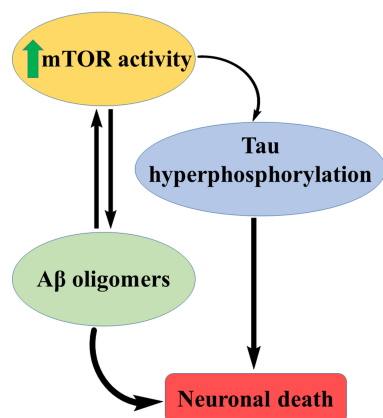


Fig. (9). mTOR in AD.

3.9. Caspases

Apoptosis shows a prime role in the proper functioning and appearance of the brain. However, inapt activation of this pathway in an ageing brain leads to the degeneration of neurons. In AD, caspases produce neurodegeneration as well as other underlying pathologies of the disease [48]. Fig. (10) exhibits the involvement of caspases in the progression of AD.

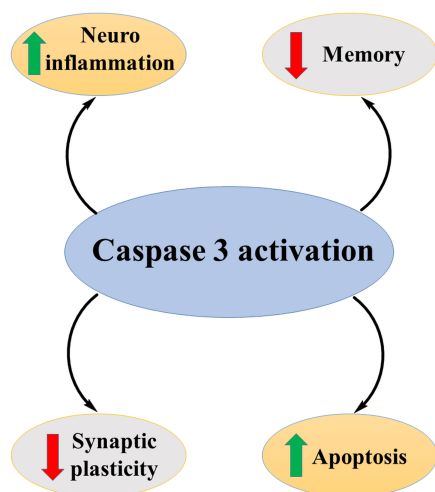


Fig. (10). Activity of caspases in AD.

Caspases are protease enzymes that facilitate programmed cell death or apoptosis. Activation of the caspase pathway facilitates a cascade of events that will promote the demolition of cell components and, ultimately, cell death. Dysregulation of caspases underlies diseases like cancer and inflammatory diseases, including AD [49].

Initiator caspases (caspases 8 and 9) eventually activate executioner caspases (caspases 3, 6 and 7) followed by coordination of their activities which lead to demolition of different proteins of cell components and finally cell death through DNA fragmentation. Most of the apoptotic programmes are executed *via* an intrinsic pathway or extrinsic pathway [50].

In AD, there is NFT formation and neuronal cell death. Amyloid precursor proteins (APP) are cleaved by the action of β and γ secretases to form $A\beta$, and this $A\beta$ oligomerizes and leads to the production of reactive oxygen species and oxidative stress and finally cell death. The formation of $A\beta$ may lead to activation of caspases, which will lead to the cleavage of different cellular proteins, mainly tau and result in the breakdown of the cytoskeleton and hyperphosphorylation of tau. As tau proteins are essential in the structural stability of neurons, hyperphosphorylation of tau leads to additional instability of the cytoskeleton. Due to hyperphosphorylation, there is an interruption of the microtubular network, which may lead to damaged axonal transport and finally cell death of neurons. Cleavage of APP produces further production of $A\beta$ [51, 52].

3.10. Ubiquitin and Autophagy

Proteins in the body may undergo mutations and misfold into another product. This mutation may lead to abnormal activities. This is probably prevented by controlling the system through different mechanisms such as ubiquitin, biological chaperons and autophagy [53]. This controlling mechanism will prevent the accretion of toxic levels of corrupted proteins by breaking them down into polypeptide chains. If this system is disturbed, it may accumulate in different parts of the body and may cause the development of neurodegenerative diseases like AD and Parkinson's disease [54].

In AD, memory loss and other behavioral changes are caused by the synthesis of defective proteins, *i.e.* APP is cleaved into $A\beta$, and later it oligomerizes and accumulates in the brain to cause neuronal death [55]. Oligomerized $A\beta$ promotes the hyperphosphorylation of tau proteins. Hyperphosphorylation of tau produces NFT, and this impairs the microtubular skeleton of the axon and leads to the damaged axonal transmission of impulses [56].

Degradation of intracellular proteins is mediated by ubiquitin proteasomal system (UPS), and the extracellular proteins by lysosomes. In AD brain, there occurs impairment of UPS, which leads to accumulation of oligomerized $A\beta$ and tau, eventually causing synaptic dysfunction in different neurological disorders like AD, Huntington's disease and Parkinson's disease [57].

Autophagy or self-eating is the process through which the lysosome removes cell debris for total degradation of damaged cell components. There are 3 types of autophagy, micro, macro and chaperone-mediated autophagy in which macroautophagy is the most prevalent one [58]. Autophagy is associated with an array of normal physiological processes as well as pathological conditions, such as development,

cell death, ageing, antigen presentation, bacterial degradation, and tumor suppression [59]. Fig. (11) shows that the impairment of autophagy is associated with AD.

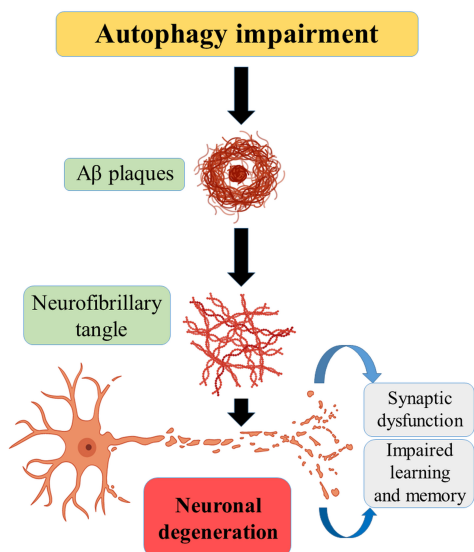


Fig. (11). Role of autophagy in Alzheimer's.

Endosomal and lysosomal pathways are involved in the regulation of levels of APP. Abnormalities in this pathway may lead to the accumulation and deposition of APP [60]. Early endosomes cleave APP into Aβ from healthy cells. An upregulation of the endosomal lysosomal path results in an increased number of lysosomes so that an increased formation of Aβ occurs. As the levels of Aβ increase, oligomerization of Aβ takes place and finally, the accumulation and formation of senile plaques [61, 62].

3.11. Polyunsaturated Fatty Acids (PUFA)

Polyunsaturated fatty acids (PUFA) have a crucial part in neuronal function, and the modification of these compounds in the brain could influence neurodegenerative diseases like AD [63]. Arachidonic acid is the second most PUFA in the brain, and it is converted into different components, which facilitate inflammation and synaptic transmission.

Studies show that various PUFA, ω-3 fatty acids like docosahexaenoic acid (DHA), eicosatetraenoic acid (EPA), and α-linolenic acid (ALA), prevent oligomerization and self-aggregation of Aβ [64]. They interact with aggregation-prone phe19- ala21 and inhibit aggregation. Nevertheless, other ω-6 PUFAs like arachidonic acid (ARA) and linoleic acid (LNA) act as proinflammatory agents and are involved in the pathology of AD. Also, ARA can boost up the production of Aβ peptides [65]. ω-9 fatty acids such as monounsaturated fatty acids (MUFA) and oleic acid (OA) may reduce the levels of Aβ42.

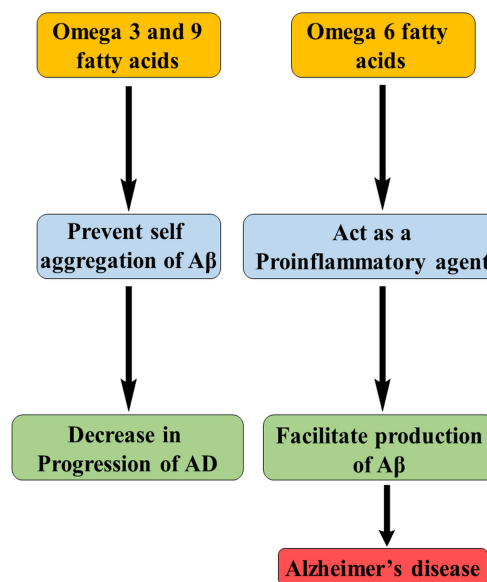


Fig. (12). PUFA and AD.

The interconnection between PUFA and AD is shown in Fig. (12). However, in recent findings, it is proven that all the PUFAs, including ARA and LNA, can prevent the aggregation of Aβ and so that they reduce the progression of AD [66].

3.12. Calcium Signaling Pathway

Calcium ion (Ca²⁺) is the significant component that modifies the function and structure of nerve cells in the brain, mainly in the neuronal growth, synaptic and cognitive function. From various studies, it is evident that Ca²⁺ homeostasis has a vital role in the progression of AD and its associated conditions, such as memory loss and cognitive impairment [67]. Whenever there is an upregulation of calcium release from the endoplasmic reticulum (ER), through ryanodine receptors (RYR), the activity of β and γ secretase increases and thereby oligomerization of Aβ leads to a progression of AD.

Fig. (13) shows the calcium homeostasis in the formation of amyloid plaques and changes in synaptic plasticity. Calcium is essential for the synaptic transmission of impulses as well as synaptic plasticity, which is responsible for learning and memory [68]. The high concentration of Ca²⁺ may lead to long-term potentiation, and small elevation may cause durable depression. In another way, Ca²⁺ can either form or remove memories. Any changes in the calcium homeostasis lead to the upsurge of apoptosis, leading to neuronal death and, thereby, dementia [69].

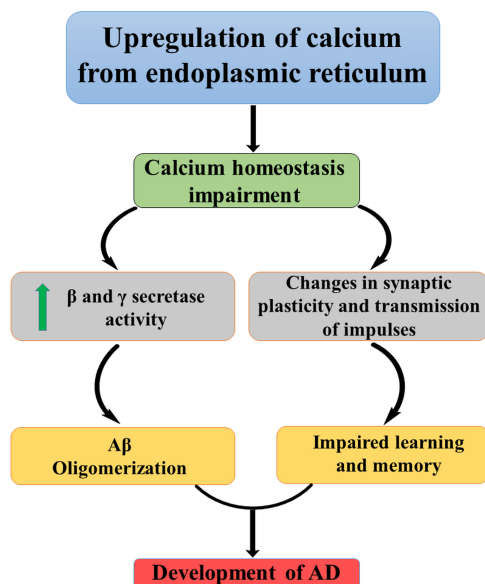


Fig. (13). Calcium in AD.

3.13. Ceramide

Ceramide is a principal component of sphingolipids and plays an essential role in vital cellular progressions like growth, cell cycle arrest, survival, and apoptosis. It is composed of a sphingosine lipid and fatty acid, which is connected by an amide bond [70]. Ceramides are suggested to be the crucial players in the pathogenesis of AD. Raised basal serum levels of ceramide species are linked with a higher risk for developing AD [71].

Recently, histopathological studies showed that AD brains have a higher number of ceramides when compared to healthy control brains. Free radicals generated by the ceramide are the principal source of neurodegeneration. With an increased level of ceramides, there may be upregulation of production of reactive oxygen species (ROS) which leads to neuronal damage *via* A β oligomerization and tau protein hyperphosphorylation. The exact role of ceramides is still uncertain [72, 73]. Safeguarding of ceramide homeostasis is essential for normal brain functioning. Studies show that dysregulation of ceramide metabolism is associated with quite a lot of pathological characteristics of AD such as A β oligomerization, tau protein hyperphosphorylation, generation of ROS, impairment of different signaling pathways, apoptosis and finally neuronal death [74, 75]. Activities of ceramides in Alzheimer's brain are portrayed in Fig. (14).

3.14. Notch Signaling Pathway

Presenilin-1 (PES-1) is one of the four core proteins in the γ secretase complex, which is considered crucial in the generation of amyloid-beta (A β) from amyloid precursor protein (APP) by γ secretase. Mutation to PES-1 is a significant source of early onset of FAD [76].

A notch signaling pathway is involved in the differentiation and development of various systems, including neuronal development. It is involved in maintaining synaptic plasticity, long-term learning and memory and neurogenesis.

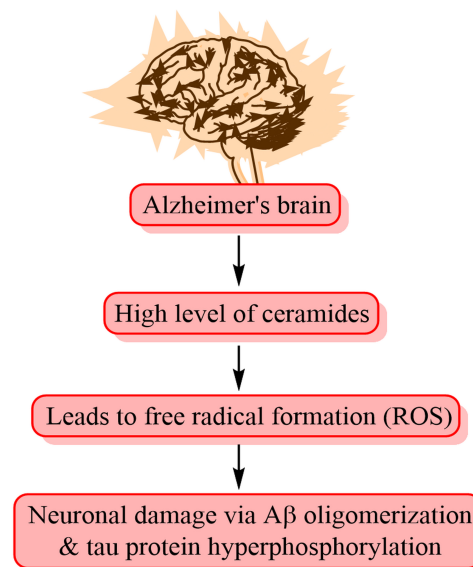


Fig. (14). Activity of ceramides in Alzheimer's brain.

The notch is a transmembrane protein and substrate of γ secretase and or PES-1 considered necessary in the progression of AD. Notch proteins interact with amyloid precursor protein (APP) as well as presenilins. Presenilins facilitate proteolysis of APP and help notch to release the Notch intracellular domain (NICD), which is essential for the notch-signaling pathway. NICD shifts into the nucleus, and this can modify transcription *via* binding with CSL, a group of DNA binding proteins [77]. Fig. (15) illustrates the role of notch signaling in AD.

Studies have shown that in a notch mutant mouse, when a loss of notch signaling function occurs, it consequently results in a long-term memory deficit. The permanent gap in notch signaling may show learning and memory impairment. From this, it is evident that notch signaling linked transcription is essential for spatial learning [78]. Notch pathway is also involved in the neuronal death, and γ secretase-facilitated notch signaling deteriorates brain damage. Because of this brain damage, ischemia and stroke, there will be an advancement in AD and vascular dementia [79].

3.15. Neurotrophins in AD

Neurotrophins are a family of proteins, which include nerve growth factor (NGF), Neurotrophin 3 (NT-3), brain-derived neurotrophic factor (BDNF) and Neurotrophin 4 (NT 4). They all bind to specific tyrosine kinase receptors (Trks), NGF to Trk A, NT 4 and BDNF to Trk B and NT 3 binds to Trk C [80, 81].

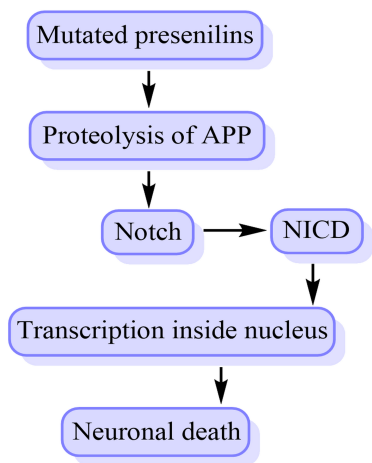


Fig. (15). Notch signaling in the progression of AD.

Pathophysiology of AD primarily focuses on BDNF and NGF. Trk A in forebrain responds to NGF, and it maintains synaptic communication with the hippocampus and cortex neurons [82]. BDNF present in the hippocampus is responsible for the synaptic plasticity of neurons and memory establishment. BDNF will bind to Trk B and is the critical component of memory formation. Therefore, any changes in the expression of NGF or BDNF or levels of subsequent receptors may result in memory deficit (Fig. 16) [83].

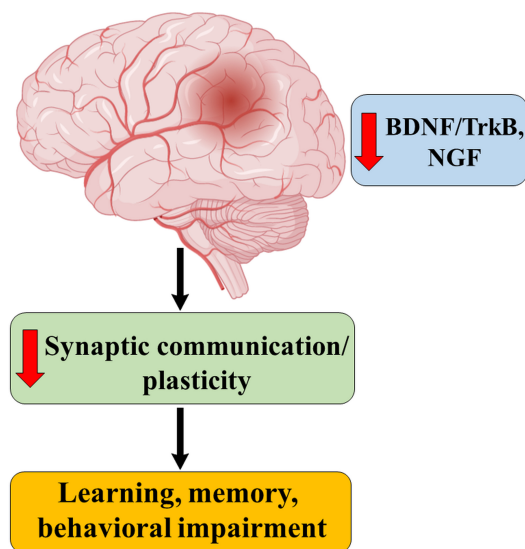


Fig. (16). Neurotrophins in AD.

3.16. BACE-1 (β APP Cleaving Enzyme-1 or β Secretase)

BACE-1 is the enzyme involved in the cleavage of APP, which is the significant step in the formation of Aβ [84, 85]. It is a transmembrane protease enzyme, which cleaves APP at its β site. After cleavage, the production of amyloid-beta takes place and oligomerization of the same produces

plaques and leads to neuronal damage and AD [86]. The inhibition of BACE 1 shows a reduced level of Aβ and effectively a better synaptic activity [87, 88], as it is related to the formation of amyloid-beta, well described in Fig. (3).

3.17. JNK and AD

c-Jun N terminal kinase (JNK) is vital in the maintenance of neuronal plasticity, cell degeneration, and regeneration. It is activated after the induction of stress factors like oxidative stress, cytokines as well as Aβ. Activated JNK is accountable for the regulation of apoptosis so that it is critical in neurodegenerative diseases like AD [89]. JNK is associated with neuronal death, amyloid-beta production and production of neurofibrillary tangles. JNK 3 is the most prominent one which responds to stress stimuli and is more expressed in the AD brain [90]. Fig. 17 highlights the relation between JNK and AD.

From studies, it is evident that there is an overexpression of phosphorylated JNK in AD brains along with Aβ plaques. Also, it promotes the formation of NFT and hyperphosphorylated tau [91, 92].

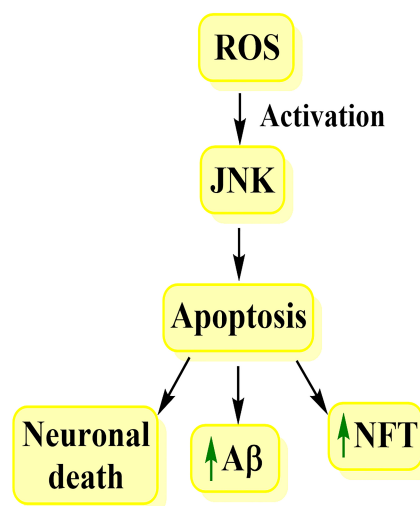


Fig. (17). JNK and AD.

3.18. Glycogen Synthase Kinase 3β (GSK 3β)

Glycogen synthase kinase is a serine-threonine kinase involved in many vital activities of the body. There are two isoforms of GSK3, namely, GSK3α and GSK3β in which GSK3β is abundantly seen and the level of the same increases with age. From various studies, GSK3β is hyperactive in AD patients. Insulin and the Wnt signaling pathway modulate the activity of GSK3β [93].

Insulin signaling facilitates PI3 kinase activation, which will eventually lead to the phosphorylation of GSK3β and GSK3α serine at positions 9 and 21 by AKT. GSK3 could also be regulated by auto phosphorylating tyrosine residue at positions 279/216, and it augments its activity [94]. Wnt sig-

naling modulates GSK3 by dislocating different binding partners that are bound to GSK3 to stimulate action and prevent phosphorylation and degradation of β catenin.

Deregulation of GSK3 leads to many pathological conditions, including neurological disorders like AD. It is involved in the hyperphosphorylation of tau proteins, inflammation and production of senile plaques by regulating APP and BACE1. GSK3 decreases the production of acetylcholine, leading to the cholinergic deficit and is involved in apoptosis by which there will be neuronal loss [95].

Studies depict the relationship between GSK3 and prenilin 1 (PS-1), and it is demonstrated in Fig. (18). Hyperactivation of GSK3 leads to a functional change in PS1. PS 1 is involved in the pathology of FAD. PS 1 is associated with the formation of a complex of β catenin and serine residues of GSK3. When there is overactivation of GSK3, it downregulates the complex and leads to changes in synaptic and neural functions and hence AD.

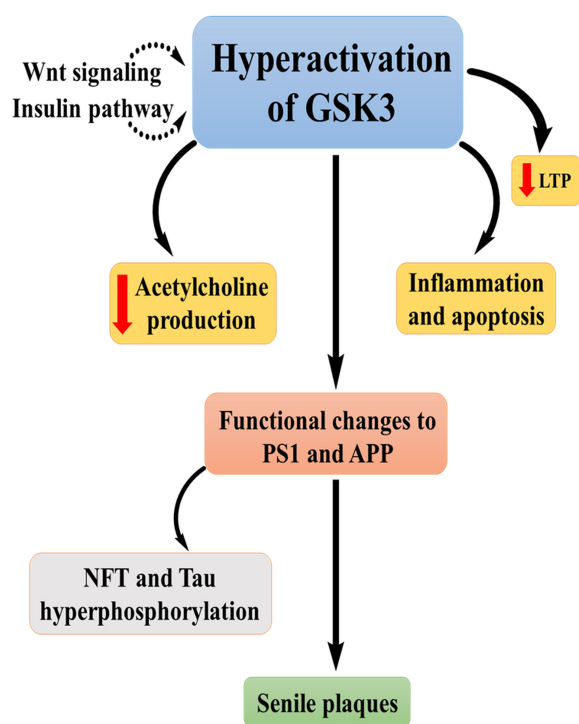


Fig. (18). Role of GSK3 β in the progression of AD.

Long-term potentiation (LTP) is associated with Wnt signaling pathway, the suppression of which declines LTP. Wnt signaling and insulin negatively regulate GSK3 and so that hyperactivation of GSK3 leads to impairment of LTP. Novel drug development, which targets GSK3, is considered to be a potential drug for AD, mood disorders, and diabetes [96]. In a recent study of a chemical moiety, benzisoxazoles were found to be a promising target as a GSK3 inhibitor [97].

4. FUTURE PERSPECTIVES

AD is the most common type of neurodegenerative disease with no cure. Accumulation of toxic proteins, including alpha-synuclein (Lewy bodies), beta-amyloid plaques, Tau tangles, and TDP-43 is considered as pathophysiology involved in neurodegeneration and these are often used as probable molecular biomarkers to predict disease progression. Significantly altered neurotransmission of dopamine and acetylcholine can also lead to neuronal degeneration.

Currently, available drugs for the treatment of AD belong to the category of either acetylcholinesterase inhibitors or NMDA glutamate receptor antagonist. These drugs are only useful during the first year of treatment for patients with mild to moderate AD and provide some degree of improvement in cognitive functions. The efficacy of these drugs declines wholly and subsequently vanishes after 2 to 3 years of treatment. The progressive loss of efficacy for these symptomatic treatments warrants the necessity of identifying newer targets for novel small molecule drug interventions.

The major difficulty in treating AD is due to the activation of several harmful processes in the brain. To effectively prevent the progress of these destructive processes in the brain, it is necessary to address them simultaneously. In case of such complex disease pathologies, single-target drugs are inadequate to achieve the desired therapeutic effect. Therefore newer multi-target drugs (MTDs) should be designed to simultaneously target several aspects of disease pathology leading to neuronal damage rather than just the symptoms currently addressed by single-target drugs. Further, it is well proven that MTDs have a better safety profile when compared to single-targeted ones.

CONCLUSION

AD is the sixth leading cause of death worldwide. It is a complex neurological disorder with learning and memory impairment and other behavioral changes. There is no such cure for the disease, and only four drugs are available in the market for symptomatic relief of this illness. Major hypotheses include the deficit of acetylcholine, the formation of A β plaques, neurofibrillary tangle formation (NFT) and hyperphosphorylation of tau proteins. Other than these hypotheses, there underlie many other pathophysiologies that modify the causes of AD.

In various studies, it is evident that there are more than 20 pathophysiological factors involved in altering this disease progression and development. Therefore, inhibition or activation of these factors could modify the advancement of AD, and those agents used for the same could be another choice of drug for the condition. These factors are all interconnected in a way or the other and imbalance of any of these may facilitate disease progression. Every one of them ends up to the same cardinal hypotheses such as the formation of senile A β plaques, tau protein hyperphosphorylation or formation of neurofibrillary tangles (NFTs).

In this review, we discuss the main pathways that underlie neurodegeneration in AD, and this could provide a thor-

ough understanding of different neurodegenerative mechanisms that help in the design and development of novel target-based small molecules for the treatment of AD.

LIST OF ABBREVIATIONS

AD	= Alzheimer's Disease
ADAD	= Autosomal Dominant Alzheimer's Disease
AChE	= Acetylcholinesterase
A β	= Amyloid-beta
APP	= Amyloid Precursor Proteins
ApoE	= Apolipoprotein
AMPK	= Adenosine Monophosphate-activated Protein Kinase
ALA	= α -linolenic Acid
ARA	= Arachidonic Acid
AKT	= Protein Kinase B
β AP	= β -amyloid Proteins
BDNF	= Brain-derived Neurotrophic Factor
BACE-1	= β APP Cleaving Enzyme 1
CNS	= Central Nervous System
CR	= Calorie Restriction
Ca ⁺	= Calcium ion
DKK-1	= Dickkopf-1
DNA	= Deoxyribonucleic Acid
DHA	= Docosahexaenoic acid
EPA	= Eicosatetraenoic Acid
ER	= Endoplasmic Reticulum
FAD	= Familial Alzheimer's Disease
GSK 3 β	= Glycogen Synthase Kinase 3 β
HDAC	= Histone D Acetylase
JNK	= c-Jun N terminal Kinase
LTP	= Long-term Potentiation
LNA	= Linoleic Acid
MAPs	= Microtubular Associated Proteins
mTOR	= Mammalian Target of Rapamycin
MUFA	= Monounsaturated Fatty Acids
NFTs	= Neurofibrillary Tangles
NMDA	= N Methyl D Aspartate
NMDAR	= N-methyl-D-aspartate Receptor

NAD ⁺	= Nicotinamide Dinucleotide
NMN	= Nicotinamide Mononucleotide
NICD	= Notch Intracellular Domain
NGF	= Nerve Growth Factor
NT-3	= Neurotrophin 3
NT-4	= Neurotrophin 4
OA	= Oleic Acid
PES	= Presenilins
PIK3	= Phosphoinositide 3 Kinase
PUFA	= Polyunsaturated Fatty Acids
PI3	= Phosphoinositide 3
PS-1	= Presenilin 1
RYR	= Ryanodine Receptors
ROS	= Reactive Oxygen Species
Trks	= Tyrosine kinase receptors
UPS	= Ubiquitin Proteasomal System
VLDL	= Very Low-density Lipoprotein

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The author Anu Kunnath Ramachandran is thankful to AICTE, New Delhi for financial assistance in the form of National Doctoral Fellowship (NDF) and another author Subham Das to Manipal Academy of Higher Education for providing Dr.T.M.A. Pai Fellowship. The authors also acknowledge with thanks, to the Manipal College of Pharmaceutical Sciences, for providing facilities for this work.

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